Evaluation and Management of Ascites

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Cirrhosis: Prevalence

• The prevalence of cirrhosis, both worldwide and in the US, is unknown
  – Compensated cirrhosis often goes undetected for prolonged periods of time

• Experts estimate that up to 1% of the population (~3 million) may have histological cirrhosis

Etiology of Cirrhosis

- Cirrhosis can result from:
  - Alcohol-related liver disease (~60% to 70% of cases)
  - Chronic hepatitis C
  - Chronic hepatitis B
  - Chronic hepatitis B and D
  - Nonalcoholic fatty liver disease (NAFLD; ~10% of cases)
  - Autoimmune hepatitis
  - Drugs, toxins, and infections

Natural History of Cirrhosis

• Once decompensation occurs, median survival is approximately 2 years

• Most commonly reported causes of death:
  – Hepatorenal syndrome
  – Sepsis
  – Variceal hemorrhage
  – HCC

Decompensated Cirrhosis

- Primary complications include:
  - Ascites
  - Jaundice
  - Variceal hemorrhage
  - Portosystemic encephalopathy

- Other possible complications include:
  - Spontaneous bacterial peritonitis
  - Hepatic hydrothorax
  - Hepatorenal syndrome
  - Portopulmonary hypertension
  - Hepatocellular carcinoma
  - Portal vein thrombosis

Diagnosis of ascites: Physical examination

- Patients with bulging abdomen should be assessed for flank dullness
- Physical exam is non-specific for ascites
  - compromised in obese patients
  - ‘shifting dullness’ most useful for clinical use
- Shifting dullness as a diagnostic tool for ascites:
  - sensitivity: 83%
  - specificity: 56%
  - negative predictive value ~90%
- Imaging is the best diagnostic tool for ascites
- Fluid wave and puddle sign are cumbersome and perform less well

Cirrhosis Is the Most Common Cause of Ascites

- Peritoneal malignancy
- Heart failure
- Peritoneal tuberculosis
- Others: Pancreatic, Budd-Chiari syndrome, Nephrogenic ascites

## Diagnosis of ascites: Differential diagnosis

<table>
<thead>
<tr>
<th>Associated with portal hypertension</th>
<th>Non-related to portal HT</th>
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</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Cancer</td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Myxedema</td>
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<tr>
<td>Heart failure</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Pericarditis with constrictive disease</td>
<td></td>
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<tr>
<td>Budd-Chiari syndrome</td>
<td></td>
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<tr>
<td>Sinusoidal obstruction syndrome / VOD</td>
<td></td>
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<tr>
<td>Presinusoidal disease</td>
<td></td>
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</tbody>
</table>

*Runyon, Hepatology 2009; 49: 2087–107*
Serum ascites albumin gradient (SAAG)

- Superior to ascites total protein for differential diagnosis
- Calculated by serum albumin – ascitic fluid albumin = SAAG (samples taken the same day)
- SAAG >1.1 g/dL indicates portal hypertension
  - >90% accuracy
- SAAG should be measured as part of initial laboratory investigations / diagnostic tests

Hoefs, J Lab Clin Med 1983; 102: 260–73
Gupta et al, J Gastroenterol Hepatol 1995; 10: 295–9
Outline

- Pathophysiology and rationale for treatment
- Diuretics
- Paracentesis and albumin
DEFINITION & CLASSIFICATION

• Non-refractory or Uncomplicated Ascites
  – Grade 1. Only detectable by US.
  – Grade 2. Moderate detectable by exam
  – Grade 3. Tense ascites

• REFRACTORY ASCITES

Portal Hypertension
No ascites

Uncomplicated ascites

Refractory ascites

Hyponatremia

1) Grade 2 - Salt restriction + diuretics
2) Grade 3 - Large volume paracentesis (LVP) plus iv. Albumin → diuretics
Management of Uncomplicated Ascites

- Diuretic Therapy
  - Dosage
    - Spironolactone 100-400 mg/day
    - Furosemide 40-160 mg/d
  - Ideal weight loss:
    - 300-500 g/day in patients without peripheral edema
    - 800-1000 g/day in patients with peripheral edema
  - Tailor therapy according to degree of sodium excretion in baseline conditions.
**Initial Management**

Grade 2 Ascites

- Low-sodium diet (80 mEq/day)
- Diuretics

- Patients without peripheral edema
  - Spironolactone or combination *prn*
  - **Goal**: Weight loss: 0.5 kg/day

- Patients with peripheral edema
  - Spironolactone + Furosemide
  - **Goal**: Weight loss: 1 kg/day

**Maintenance Therapy**

- Continue low-sodium diet
- Reduce diuretic therapy as needed

GRADE 3 ASCITES

Large-Volume Paracentesis (LVP) → Diuretics

• LVP
  – Faster resolution of ascites (of particular relevance in hospitalized patients) compared with diuretics
  – Fewer complications
  – Post paracentesis circulatory dysfunction
    • 50% increase in renin activity over baseline at day 6 after LVP

Grade 3 Ascites

Initial Management

LARGE-VOLUME PARACENTESIS

< 5 liters

Synthetic plasma expanders (8 g/L of ascites tapped)

> 5 liters

Albumin (8 g/L of ascites tapped)

Maintenance therapy

Low-sodium diet (88 mEq/day)
Diuretic therapy

REFRACTORY ASCITES
(International Ascites Club Definition)

Diuretic-resistant

– Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to a lack of response to sodium restriction and diuretic treatment (spironolactone 400 mg/day and furosemide 160 mg/day)

Diuretic-intractable

– Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to the development of diuretic-induced complications that preclude the use of an effective diuretic dosage

REFRACTORY ASCITES - Survival

Refractory Ascites

LVP plus albumin (6-8 g/L)

First step of management

Low-sodium diet
Fluid restriction in hyponatremic patients

Maintenance therapy

Ongoing LVP with Albumin

Preserved liver function?
No contraindication?

Yes
Consider TIPS

No
Continue large-volume paracentesis

TIPS Considerations for Ascites

• Frequent LVP
• Cardiac clearance
• Preserved renal function
• No significant history of HE
• Reasonable hepatic synthetic function
• Interventional radiology expertise
TIPS AND ASCITES

Beneficial effects
- Improves sodium excretion and reduces ascites volume and diuretic requirements
- Improves renal function in patients with HRS

Problems
- Frequent obstruction
- High incidence of encephalopathy
- Increased mortality in Child C patients
- High cost
- Need expertise
Who?
Bili < 3 mg/dL
Sodium > 130 mEq/L
MELD <18
Age < 70
Loculated ascites
No cardiac disease
No pulmonary hypertension
No HCC
**TIPS: Potential complications**

- Increased risk of new / worsening HE
  - 20–30% incidence
  - by meta-analysis RR 2.25 (D’Amico et al)

- Stenosis
  - reduced by use of coated stent

- Dislocation of stent
  - very rare

- Intravascular hemolysis

- Perforation of liver surface with intraperitoneal bleeding

- Cardiac failure
  - 2.5%

- Renal failure
  - 4.3%

- Liver failure
  - ~1.9%; more frequent in patients with advanced liver dysfunction (e.g., Child Pugh Score >11; MELD >18)

- Bacterial infection of stent
  - ~1.5%

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Salerno et al, Liver Int 2010; 30: 937–47
Incidence of HE after TIPS

- n=78 patients undergoing TIPS
- 19.9 months' follow-up
- HE in 35/78 (44.8%)
  - refractory HE in 8% of patients
- 89 episodes of HE
  - 55% grade III-IV

Riggio et al, Am J Gastroenterol 2008; 103: 2738–46
Impact of beta blockers on survival in patients with refractory ascites

- Single center observational study
  - refractory ascites: Diuretic-resistant (n=47) or intractable (n=104)

![Survival graph]

<table>
<thead>
<tr>
<th>Survival</th>
<th>Beta Blockers (n=77)</th>
<th>No beta blockers (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>5 months</td>
<td>20 months</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1 year</td>
<td>64%</td>
<td>19%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 years</td>
<td>45%</td>
<td>9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Serste et al, Hepatology 2010; 52: 1017–22
Increased mortality in cirrhotic patients receiving beta-blockers: Potential mechanisms

- In the study by Serste, 79.5% of cases with an identified cause of death, died of sepsis.
- Norepinephrine can be increased by beta-blocker therapy and liver dysfunction.
- Ammonia levels also increase with worsening liver function.
  - also increased by propranolol.
- Both ammonia and norepinephrine impair neutrophil function.
  - an underlying contribution to mortality?
- This requires further research and also confirmatory data.

*Kalambokis et al, Hepatology 2011; 54: 1486-7*
Spontaneous bacterial peritonitis

- ~30% of patients with ascites develop SBP\textsuperscript{1–2}
- Diagnostic criteria
  - ascites fluid with $\geq 250$ neutrophils/mm\textsuperscript{3}
  - culture may be negative
- Distinguish from intra-abdominal infection due to perforated viscus or abscess, which is characterized by
  - multiple organisms on gram stain or culture
  - elevated LDH, total protein $>1$ g/dL, glucose $<50$ mg/dL
    (sensitive but not specific for secondary cause)
- Recurrence rate: 55% in 1 year
- Approximately one-third of patients may develop hepatorenal syndrome

Perumalswami & Schiano, Dig Dis Sci 2011; 56: 1266–81
Primary prophylaxis recommended for patients with ascites (protein <1.5 mg/dL) plus one or more of:

- creatinine \( \geq 1.2 \text{ mg/dL} \)
- urea \( \geq 25 \text{ mg/dL} \)
- sodium \( \leq 130 \text{ mEq/L} \)
- Child-Turcotte Pugh \( \geq 9 \) with bilirubin \( \geq 3 \text{ mg/dL} \)

Albumin to prevent renal failure if bilirubin >4 mg/dL or creatinine >1 mg/dL

- 1.5 g/kg within 6 hours of diagnosis and 1.0 g/kg on day 3

Long-term prophylaxis (primary or secondary) consists of a daily quinolone (norfloxacin) or less commonly TMP/SMX

*Runyon, Hepatology 2009; 49: 2087–107*
Antibacterial prophylaxis in patients with GI bleeding

- Variceal bleeding is a major risk factor for SBP\(^1\)

- Antibiotic prophylaxis reduces risk of SBP, by meta-analysis, relative risk of SBP = 0.29 (0.15–0.57)\(^2\)

\(^1\)Biecker, World J Gastroenterol 2011; 17: 1237–48

\(^2\)Chavez-Tapia et al, Cochrane Database Syst Rev 2010; 9: CD002907
Antibiotic resistance

- Rapid emergence of norfloxacin resistance
  - may not be associated with clinically significant infection

- Over a 2-year follow-up of patients receiving norfloxacin for >1 month
  - 63/172 (37%) gram negative isolates resistant to quinolones
  - 84/172 (49%) gram negative isolates resistant to TMP/SMX

- Resistant bacterial strains more common in patients receiving prophylaxis

- Selection of patients for prophylaxis is therefore important

Segarra-Newnham & Henneman, Ann Pharmacother 2010; 44: 1946–54
Impact of albumin infusion on outcomes of patients with SBP

Albumin dose: 1.5 g/kg at time of diagnosis, 1 g/kg on day 3